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REMARKS

Claims 13, 14 and 18-31, all the claims currently in this application, have been rejected on substantive grounds, under 35 U.S.C. §103(a), as being unpatentable over U.S. Patent No. 5,304,687 to Bargiotti et al. taken with Kuhl et al., Cancer Chemo. Pharma., 33, 10-16 (1993), Nakamura et al., Gan. To Kagaku Ryoho, 8 Pt 2, 2562-2567 (August 15, 1988) (English Abstract) and Gorbunova, "Intrahepatic Arterial Infusion Chemotherapy for Primary and Metastatic Cancer of the Liver," (1990).

The Official Action avers that Bargiotti et al. is drawn to morpholino derivatives of anthracyclines including methoxy morpholino doxorubicin (MMDX). The Official Action submits that these derivatives are shown to inhibit solid tumors, such as human carcinoma, with intravenous and oral administration. The Official Action admits that Bargiotti et al. does not disclose the administration of MMDX by intrahepatic introduction.

The secondary Kuhl et al. reference, the Official Action avers, is drawn to doxorubicin derivatives. That reference teaches that one such derivative, MMDX, has broad-spectrum antitumor activity and is non-cross-resistant in multidrug-resistant tumor models. The Official Action further submits that MMDX is activated in the liver to a metabolite which crosslinks to DNA and is 10 times more potent than doxorubicin.

The Nakamura et al. English language abstract teaches that intra-arterial infusion of lipiodol (iodized oil) and adriamycin showed remarkable therapeutic effects for advanced cancer.

The English language abstract of Gorbunova, the Official Action concludes, teaches that intra-hepatic arterial infusion chemotherapy allows for creating a super high concentration of an antitumor agent in the organ affected by the tumor.

From the above allegations of the teachings of the four applied references, the Official Action concludes that it would be obvious to a skilled artisan to make a composition comprising MMDX with iodized oil and use the same in the treatment of human liver tumors.

Applicants have carefully considered this ground of rejection and have gone so far as to obtain an English language translation of the Nakamura et al. article. That English translation is enclosed herewith. It is requested that that translation be substituted for the English language abstract currently of record in the file of the present application. Applicants conclude, after considering each of these references in detail, that the combined teaching of the applied references suggests neither the composition of Claims 12 and 13 nor the method of treating a human liver tumor as set forth in Claims 18-31.

The principal Bargiotti et al. reference indeed discloses MMDX. However, this is a generic disclosure of that compound. The utility advanced in support of the claims of this patent directed to MMDX, is the generic recitation of antitumor activity of tumors in murine, e.g. rats and mice, animals. Bargiotti et al. specifically provides experimental data establishing improved cytotoxicity and antitumor activity over doxorubicin in mice.

The above summary of the teaching of Bargiotti et al. emphasizes the lack of any disclosure of utilization of intrahepatic local infusion of MMDX in treating liver

tumors. Indeed, no disclosure of the treatment of specific liver tumors is so much as mentioned in this reference.

The secondary Kuhl et al. reference, a complete copy of which was forwarded to the USPTO in response to the August 26, 2004 Official Action, discloses the use of MMDX in the treatment of blood tumors, as demonstrated by in vitro experimentation. Those skilled in the art are aware that in vitro data supports potency of a drug, in this case MMDX, but not efficacy. That is, the absence of in vivo data evidences the absence of any teaching of efficacy of MMDX in the treatment of leukemia in animals.

It is furthermore emphasized that the experimentation reported in Kuhl et al. is limited to the treatment of leukemia, a blood tumor. The treatment of blood tumors is remarkably different from the treatment of solid tumors of the type found in the liver. Applicants have previously submitted a reference, "Cancer, Principle and Practice of Oncology," 6th Ed., DeVita et al., wherein it is taught that agents useful in the treatment of blood tumors, such as leukemia and lymphoma, have no therapeutic efficacy against solid tumors. That reference further emphasizes another principle of oncology practice. Chemotherapeutic agents, such as MMDX, are tumor-specific and the results of chemotherapy depend on tumor growth characteristics and on the tumor's individual resistance to the drug.

The above remarks establish that the combined teaching of Bargiotti et al. and Kuhl et al. do not so much as suggest a pharmaceutical composition which comprises MMDX and a pharmaceutically acceptable agent which remains selective in a liver tumor, as set forth in Claims 13 and 14. The combined teaching of Bargiotti et al. and

Kuhl et al. are even more remote from the method of Claims 18-31. Claims 18-31 require the intrahepatic administration of a therapeutically effective amount of MMDX. Neither of these two references so much as suggest treatment of liver tumors by administration of MMDX, let alone intrahepatic introduction of that drug.

The Nakamura et al. article discusses clinical trials concerning the intrahepatic introduction of doxorubicin hydrochloride and iodized oil in the treatment of liver tumors. As such, one would expect that this reference would be highly relevant to the claims of the present application. In fact, Nakamura et al. is clearly distinguished from the claims of the present application.

The third applied reference, an English translation of the full Nakamura et al. teaching is directed to doxorubicin, which is a clearly distinguished chemical entity from MMDX. Indeed, this fact is established by the Bargiotti et al. reference which compares MMDX with doxorubicin, concluding that MMDX provides improved cytotoxicity and antitumor activity over doxorubicin based on in vivo testing of mice. It is emphasized that Nakamura et al. provides no teaching or suggestion of utilization of MMDX in the treatment of liver tumors. Indeed, there is not so much as a mention of MMDX in the Nakamura et al. article.

The above analysis of Nakamura et al. emphasizes its close similarity to the teaching of the Russian language Gorbunova article. Gorbunova et al. discloses intrahepatic arterial infusion chemotherapy in primary and metastatic cancer of the liver. Like Nakamura et al., it is limited to the administration of doxorubicin. As such, Gorbunova, like Nakamura et al., provides no disclosure, teaching or suggestion of utilizing MMDX, the only chemotherapeutic agent recited in the treatment of liver

tumors in any of the claims of the present application. Indeed, it is less pertinent to the dependent claims of the present application than is even Nakamura et al., given the fact that Gorbunova lacks any disclosure of utilization of iodized oil.

The above remarks, emphasizing the clear line of distinction between doxorubicin and MMDX, was exhaustively discussed and emphasized in applicants' response filed March 12, 2004. Thus, the tertiary Nakamura et al. and Gorbunova references add nothing to the clear insufficiency of the combined teaching of the primary and secondary Bargiotti et al. and Kuhl et al. references.

The above remarks emphasize the total failure of the applied reference to make obvious any of the claims currently in this application. This discussion does not begin to address the dramatic contribution to the art embodied by the claims of the present application. Those skilled in the art are aware of the prejudice, prior to the invention embodied by the claims of the present application, against intra-arterial administration of anthracyclines metabolized in vivo into cytotoxic derivatives.

Attention is directed to the technical article Robert et al., Cancer Surveys, 17, 219-252 (1993). Therein, it is clearly stated that intra-arterial administration of anthracyclines can result in a systemic exposure to active and toxic metabolites even greater than that observed with intravenous administration.

As explained in the specification of the present application, at Page 2, lines 10-19, MMDX, employed in the present application, is highly potent when administered in vivo and its cytotoxic activities increases in vitro in the presence of liver microsomes. This suggests that MMDX is transformed in the body into highly cytotoxic metabolites. Specifically, MMDX is converted in vivo to the corresponding 13-dihydro

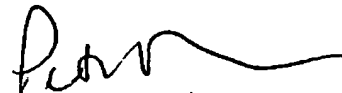
derivative, having an activity and a toxicity that is ten-fold higher than that of doxorubicin. As such, one skilled in the art, in view of the prior art teachings regarding this subject, would not have been motivated to even attempt to utilize MMDX for intrahepatic treatment of liver tumors since this drug, like other anthracyclines, such as idarubicin and iododoxorubicin, mentioned in the Robert et al. article, were earlier taught to be converted in the liver into toxic metabolites in greater concentration than even that observed with intravenous administration.

Stated differently, the knowledge in the art, evidenced by the Robert et al. article, was that intra-arterial administration of anthracycline drugs was ineffectual and indeed counter-productive in the treatment of liver tumors. The evidence of the two aforementioned anthracyclines in the clinical trials documented by Robert et al. suggested the non-effectiveness of such a method. That the claimed method of the present application is directed to this strategy evidences that the claims of the present application teach away from the teaching of the prior art. An invention teaching away from the prior art is evidence of its unobviousness.

The above remarks establish the patentable nature of all the claims currently in this application. Reconsideration and removal of the rejection of record is therefore deemed appropriate. Such action is respectfully urged.

The above remarks emphasize the patentable nature of all of the claims currently in this application. Notice of Allowance and passage to issue of these claims, Claims 12, 13 and 18-31, is therefore respectfully solicited.

Respectfully submitted,



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